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The Staudinger reaction of imines derived from 7-oxanorbornenone: formation of spiranic oxazinone versus β-lactam rings†

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Abstract—The Staudinger reaction of imines derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides afforded *spiro*-β-lactams albeit with an unexpected stereochemistry. This was not the case with arylacetic acid chlorides, which gave rise to spiranic oxazinone rings as well as the expected β-lactams. © 2002 Elsevier Science Ltd. All rights reserved.

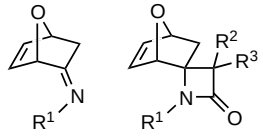
The importance of β-lactams for the treatment of bacterial infections has been amply established.[1,2] Large efforts have been made for the synthesis and structural modification of the β-lactam nucleus to increase antimicrobial activity. However the rapid emergence of bacterial strains resistant to most generally used members of this class of compounds requires a continuous effort for the design and synthesis of novel derivatives that are stable to β-lactamases and possess high potency and broad spectrum activity both in vitro and in vivo. Apart from their therapeutic utility, β-lactams are versatile synthons for the preparation of α- and β-amino acids.[2] These compounds have been considered as β-turn mimetics[3] and constitute appropriate starting materials for the synthesis of β-aminoacids with αα-cyclic disubstitution.[4]

Although a great deal of functionalized monocyclic β-lactams have been reported, relative few efforts have been devoted to the synthesis of *spiro*-β-lactams.[5] Among the different strategies developed for the construction of β-lactams,[6] the reaction of acid chlorides with imines (Staudinger reaction)[7] constitutes one of the most popular procedures.

Imines **1** derived from 7-oxanorbornenone[8] (Scheme 1) may constitute an interesting starting material for the synthesis of a new class of *spiro*-β-lactams such as **2**. Furthermore, in these structures, the inherent reactivity of the 7-oxanorbornenone framework[9] can be combined with the synthetic versatility of the β-lactam moiety in a single compound. Considering that, to the best of our knowledge, the Staudinger reaction of compounds **1** has not been previously reported, in this paper we wish to account for the first results in this field.

Treatment of compounds **1** with the arylacetic acid chlorides **3** in the presence of Et_3N (toluene, rt) did not afford the expected β-lactams (Scheme 2). Instead, the epimeric oxazinones **4** and **5** were the only reaction products.[10] The results are gathered in Table 1.

The stereochemical outcome of the reaction was dependent on the electronic nature of the aromatic moiety. Thus, in the case of compound **3a**, the reaction with imine **1a** gave rise exclusively to compound **4** whereas for compounds **3b** and **3c** the corresponding oxazinones **4** and **5** were obtained as a



Scheme 1.

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† Dedicated to Professor Henry Rapoport. '*In Memoriam*'.

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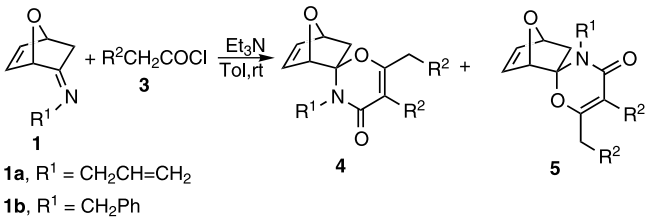
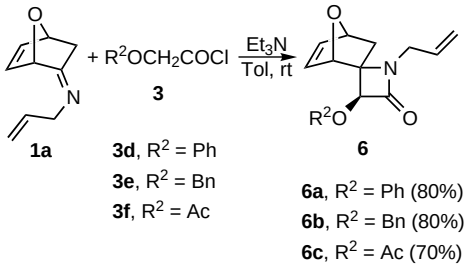


Scheme 2.

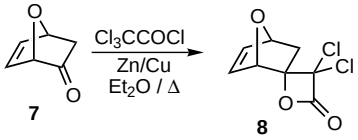


Scheme 3.

diastereomeric mixtures, although compounds **4b**,**c** were the majoritary ones. Also, the nature of the substituent R^1 attached to the nitrogen atom played an important role on the stereochemical course of the reaction (see entries 1 and 5). Finally, no improvement in yield or selectivity was observed when the reaction was carried out with an excess of acyl chloride (entries 1 and 4)

Contrary to the arylacetic derivatives **3a**–**c**, the Staudinger reaction of compounds **1a** with the 2-alkoxyarylacetic derivatives **3d**–**f**, under the same reaction conditions, afforded β-lactams **6** (Scheme 3).[11] These were obtained as single diastereomers, and no traces of the corresponding isomeric *exo*-β-lactams **2** (Scheme 1) or oxazinones were detected in the crude reaction products.

It is worth mentioning that this stereochemical outcome of β-lactam formation with acid chlorides **3d**–**f** under Staudinger reaction conditions was opposite to the one expected from a *simple* [2+2]-cycloaddition reaction,[12] which should have taken place from the *exo* face of compound **1** giving rise to compounds **6**.[13] As a matter of fact, reaction of ketone **7** with dichloroketene gave rise to the corresponding *exo*-β-lactone **8** (Scheme 4).[14]



Scheme 4.

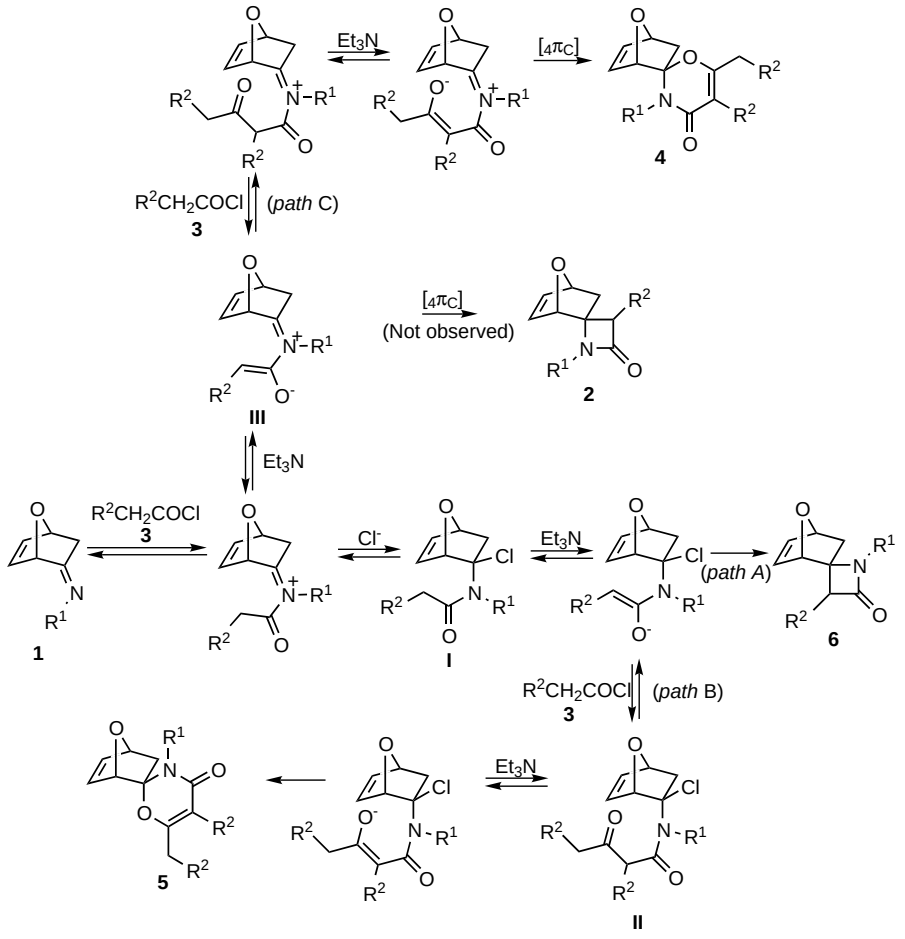
Table 1. Reactions of imines **1** with acyl chlorides **3**

No.	**1**	**3**[a]	Ratio **5**:**4**[c]	Yield (%)[d]
1	**1a**	**3a**, R^2 = Ph	0:100	50
2	**1a**	**3b**, R^2 = *p*-MeO-C_6H_4	40:60	45
3	**1a**	**3c**, R^2 = *p*-F-C_6H_4	30:70	45
4	**1a**	**3a**, R^2 = Ph[b]	0:100	55
5	**1b**	**3a**, R^2 = Ph	30:70	55

[a] All reactions were carried out using 1.5 equiv. of acyl chloride and 3 equiv. of Et_3N unless otherwise stated.
[b] In this case 2 equiv. of acyl chloride were used.
[c] Determined by integration of the ^1H NMR spectra of the crude reaction products.
[d] Combined isolated yield of **4** and **5**.

The outcome of the reaction of compounds **1** with acid chlorides **3** has been tentatively understood as outlined in Scheme 5. Initial acylation of imines **1** followed by an addition of chloride ion[13] from the *exo*-face of the iminium ion should render intermediate **I**. Enolization followed by intramolecular *endo*-displacement of chloride should render β-lactams **6**. This is the reaction pathway (path A) observed for the highly reactive oxygen-substituted enolates (R^2 = OBn, OPh, OAc).[15] On the other hand, the less reactive arylacetic enolates (R^2 = Ph, *p*-MeO-C_6H_4, *p*-F-C_6H_4) may become *C*-acylated prior to ring closure giving rise to intermediates **II** (path B). These would lead to the formation of compounds **5** via intramolecular displacement of chloride. However, participation of the iminium ion **III** followed by *C*-acylation, enolization and [4π]-conrotatory cyclization (path C) would account for the preferential formation of oxazinones **4** as major compounds.

In conclusion, the Staudinger reaction of imines derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides affords the corresponding *spiro*-β-lactams but with an unexpected *exo* stereochemistry. On the other hand, the reaction with arylacetic acid chlorides leads to spiranic oxazinone rings instead of the expected β-lactams. These compounds are obtained as mixtures of epimers, depending on the substituents of the aromatic rings and on the nitrogen atom. Further insight into this dichotomic reaction course as well as synthetic applications of these findings are in progress and will be reported in due course.



Scheme 5.

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10. The structural assignment of compounds **4** and **5** was achieved by inspection of the CH_2-N signals in their ^1H NMR spectra. It was found that when the allyl chain R^1 was in an *exo* relative position (compounds **5**), both hydrogens were grouped together (2H, $\delta = 4.10$–4.15 ppm). However, when the allyl chain was in an *endo* relative position (compounds **4**) the corresponding AB part of the CH_2 system exhibited the shielding of one of

the hydrogen signals (1H, $\delta = 4.70$–4.80 ppm and 1H, $\delta = 3.05$–3.10 ppm). This can be accounted for by a shielding effect of the C5–C6 double bond of the oxabicyclic moiety.

11. Different behaviour of alkyl and alkoxyacetyl chlorides in the Staudinger reaction has been previously reported. See: Georg, G. L.; He, P.; Kant, J.; Wu, Z. *J. Org. Chem.* **1993**, *58*, 5571 and references cited therein.
12. The stereochemistry at C-3′ of the β-lactam moiety was deduced from NOE measurements. Thus, saturation of H-3′ ($\delta = 4.50$ ppm, s) in **6b** gave rise to a 3% NOE in H-3_{endo} ($\delta = 1.60$ ppm, d, $^2J = 12.5$ Hz). No NOE was observed with H-3_{exo}. The spatial proximity of H-3′ and H-3_{endo} in **6b** (2.4 Å) was deduced from AM-1 calculations. On the other hand, a distance of 3.4 Å was found between H-3′ and H-3_{exo}.
13. *exo*-Addition is the characteristic reaction way of the carbonyl group of the derivatives of 7-oxanorbornen-5-one. See Ref. 9.
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